BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12319

European Medicines Agency initiatives and perspectives on pharmacogenomics

Falk Ehmann, Laura Caneva & Marisa Papaluca

European Medicines Agency, 7 Westferry Circus, London E14 4HB, UK

Correspondence
Dr Falk Ehmann, MD, PhD, European Medicines Agency, 7 Westferry Circus, London E14 4HB, UK.
Tel.: +44 207 523 7310
Fax: +44 207 418 8613
E-mail: falk.ehmann@ema.europa.eu

BJCP Special Issue: pharmacogenomics and pharmacoepigenetics

Keywords
European Medicines Agency, guidance, pharmacoepigenetics, pharmacogenomics, regulator

Received
29 April 2013

Accepted
19 December 2013

Accepted Article Published Online
17 January 2014

Pharmacogenomics, the study of variations of DNA and RNA characteristics as related to drug response, has become an integral part of drug development and pharmacovigilance, as reflected by the incorporation of pharmacogenomic data in EU product information. In this short review article, we describe recent European Medicines Agency initiatives intended to support further the implementation of pharmacogenomics in drug development and surveillance so that patients and the public can benefit from advances in genomic science and technology.

European Medicines Agency initiatives to enable the potential of pharmacogenomics

The International Conference of Harmonisation (ICH) E15 guideline [1] describes pharmacogenetics (PG) as a subset of pharmacogenomics (PGx) and defines it as 'the study of variations in DNA sequence as related to drug response'. A significant number of all medicinal products authorized by the European Medicines Agency (EMA) contain pharmacogenomic information in their product information [Summary of Product Characteristics (SmPC)] [2]. An analysis of the medicinal products evaluated according to the EMA centralized procedure between October 1995 and October 2013 has shown that out of 534 products, 24 products contain PGx information in the SmPC section describing the Therapeutic indications, 29 in the Posology and method of administration section and 30 in Contraindications section. In total, around 15% of products contain PGx data in the product information that directly impact patient treatment (i.e. SmPC section 4.1, 4.2 and 4.3; see Table 1), demonstrating that pharmacogenomics has become an integral part of the development and postauthorization (marketing) phase for a number of medicines, with significant impact on the management of their benefits and risks in clinical use.

In order to further promote the scientifically sound integration of pharmacogenomics in product development and to ensure that genomics is given due consideration in patient treatment, the EMA set recommendations and requirements for the investigation and incorporation of pharmacogenomics in drug development [3] and surveillance (pharmacovigilance) [4].

The EMA published its first PG guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products in 2012.

- This guideline requires that pharmacogenetic studies are carried out if *in vitro* and/or clinical (*in vivo*) studies indicate that a known functionally polymorphic enzyme or drug transporter is either likely to be important in the metabolism and elimination of the drug or likely to represent an important factor in the formation, elimination or distribution of a pharmacologically active or toxic metabolite. Furthermore, if clinical studies indicate that differences in pharmacokinetic (PK) properties cannot be explained by other intrinsic or extrinsic factors and are

Table 1

Pharmacogenomic information in the Therapeutic indications, Posology and method of administration and Contraindications sections of the Summary of Product Characteristics (SmPC) for drugs authorised by the European Medicines Agency

Pharmacogenomic information	INN/active substance (ATC class)
SmPC section: Therapeutic indications (Section 4.1)	
HLA-B*5701	Abacavir, abacavir/lamivudine, abacavir/lamivudine/zidovudine (J)
CD30	Brentuximab vedotin (L)
HER2	Everolimus, trastuzumab-docetaxel, lapatinib, pertuzumab, trastuzumab emtansine (L)
RAS	Panitumumab, cetuximab (L)
EGFR	Cetuximab, gefitinib, erlotinib, afatinib (L)
ALK	Crizotinib (L)
BRAF V600	Vemurafenib, dabrafenib (L)
BCR-ABL	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib (L)
Kit CD117	Imatinib (L)
CFTR *G551D*	Ivacaftor (R)
FIP1L1-PDGFR	Imatinib (L)
T315I	Ponatinib (L)
RET mutation*	Vandetanib (L)
PML/RAR-α t(15;17) translocation	Arsenic trioxide (L)
SmPC section: Posology and method of administration (Section 4.2)	
CYP3A4	Ranolazine (C) Darifenacin hydrobromide, fesoterodine, sildenafil, vardenafil (G) Maraviroc (J) Axitinib, ruxolitinib, cabazitaxel, sirolimus, sunitinib, erlotinib (L) Zonisamide, aripiprazole (N) Ivacaftor (R)
CYP3A5	Axitinib (L)
P-gp	Ranolazine (C)
CYP2D6	Darifenacin hydrobromide (G) Gefitinib (L) Aripiprazole, vortioxetine (N)
CYP2C9	Gefitinib (L)
RAS	Cetuximab, panitumumab (L)
HER2	Trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine (L)
BCR-ABL	Dasatinib, bosutinib, (L)
EGFR	Erlotinib, afatinib (L)
ALK+	Crizotinib (L)
BRAF V600	Vemurafenib, dabrafenib (L)
CFTR *G551D*	Ivacaftor (R)
SmPC section: Contraindications (Section 4.3)	
P-gp	Aliskiren/hydrochlorothiazide, aliskiren/amlodipine/hydrochlorothiazide, lomitapide (C)
CYP3A4	Dronedarone, ivabradine, ranolazine (C) Darifenacin, fesoterodine, sildenafil, vardenafil (G) Telithromycin, voriconazole, posaconazole, indinavir, nelfinavir, fosamprenavir, atazanavir sulfate, efavirenz/emtricitabine/tenofovir disoproxil (J) Telaprevir, boceprevir, tipranavir, darunavir, ritonavir, emtricitabine/rilpivirine/tenofovir disoproxil (J)
CYP2D6	Ritonavir (J)
DPD	Capecitabine (L)
RAS	Cetuximab, panitumumab (L)
OCT2	Fampridine (N)

Abbreviations are as follows: ALK, anaplastic lymphoma kinase; *BRAF V600*, mutation of valine 600 in the serine–threonine kinase *BRAF*; CFTR *G551D*, *G551D* mutation in the CFTR gene; C, cardiovascular system; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; G, genitourinary system and sex hormones; HER2, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; Kit, receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene; J, anti-infectives for systemic use; KRAS, Kirsten rat sarcoma 2 viral oncogene homologue; L, antineoplastic and immunomodulating agents; N, nervous system; OCT2, organic cation transporter 2; P-gp, P-glycoprotein; Ph^+ ALL, philadelphia chromosome-positive acute lymphoblastic leukaemia; Ph^+ CML, philadelphia chromosome-positive chronic myelogenous leukaemia (CML); R, respiratory system; SmPC, summary of product characteristics; X/Y indicates co-active substances in one product. *Clear warning statement on the decreased benefit of treatment for patients lacking the *RET* mutation is present in Section 4.4 as well as a recommendation for performing *RET* mutation testing.

likely to influence the efficacy or safety of the drug, follow-on investigations are mandatory.
- Follow-up pharmacogenetics investigations are recommended where available *in vitro* data indicate that a polymorphic enzyme or drug transporter contributes in a quantitatively lesser role to the PK properties of the active substance, or if there is high interindividual variation in PK that could influence safety and/or efficacy, or if major unexplained PK differences have been measured between ethnic groups.
- Prospective banking of DNA for genotype analyses is recommended in all clinical phases of development, even when there are no obvious indications of a relevant genetic influence on PK.

Analogous guidance has been drafted in the USA and Japan, and a comparison demonstrates that the EMA recommendations are unique in providing *in vitro* and *in vivo* cut-off values to guide industry drug development [5].

As this EMA guideline applies particularly to new drugs that are under development, its implementation should help to ensure that genetic variants affecting drug PK properties are investigated and their impact on benefit–risk is assessed before future drug authorization. However, older drugs, such as warfarin, acenocoumarol, codeine, tramadol and clopidogrel, have been subject to pharmacogenomic scrutiny by the EMA after their authorization [6].

At time of marketing authorization, information on the safety of a drug is necessarily limited due to relatively low exposure in clinical trials with their well-defined inclusion criteria and conditions for drug treatment. Rare but serious adverse drug reactions are often identified after marketing authorization and increased population exposure. Such adverse reactions can be linked to polymorphisms, e.g. risk of agranulocytosis due to increased exposure levels in patients treated with mercaptopurine with little or no inherited thiopurine methyl transferase (*TPMT*) activity [7]; drug interactions, e.g. higher adverse event rates in patients treated with clopidogrel with reduced CYP2C19 function due to lower active metabolite and diminished antiplatelet responses [8]; or genetic predisposition to drug-related immune responses, e.g. abacavir hypersensitivity reaction associated with carriage of the HLA-B*5701 allele [9].

Therefore, increased consideration of pharmacogenomics in the postauthorization phase of medicines, ensuring an appropriate uptake of genomics in pharmacovigilance, is desirable and has led the EMA to draft a second guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products [4].

- This guideline requires the systematic inclusion of pharmacogenomics considerations in the Risk Management Plan (RMP) for targeted therapies. For products that encompass subpopulations with genetic polymorphisms, various key elements are discussed. The guideline provides requirements for postauthorization genomic data monitoring and collection, either to confirm appropriate dose and/or co-medication or to provide advice based on identified genomic biomarkers.
- Guidance is also given on the collection and storage of genomic biospecimens during clinical trials and upon the occurrence of serious adverse reactions during postauthorization or lack of effectiveness or unexpected worsening of the condition.
- Consideration on the level and type of evidence for identification of signals, and how to report to the competent authorities [e.g. in RMP updates, PSURs (Periodic Safety Update Reviews) and published studies] is provided.
- Finally, the impact of genomic-based risk-minimization measures on Product Information is discussed.

It is too early to measure the impact of these guidelines. Their implementation during drug development and surveillance is critical for the integration of pharmacogenomic recommendations in product information (SmPC) and, consequently, patient care. As the guidelines refer to rapidly evolving science and technologies, it is recommended for companies with drugs currently under development to engage with the regulators from an early stage.

To facilitate such early dialogue, the EMA established the Innovation Task Force (ITF) [10], a multidisciplinary platform offering briefing meetings on emerging science [11], i.e. innovative products and emerging technologies [12]. These free-of-charge meetings with experts of the European Network are preparatory to formal decisions in drug development and provide a soft-landing zone in the regulatory environment. Formal advice during drug development can be sought via the scientific advice procedure [13].

The EMA further supports research into the use of biomarkers and novel methods in the development of medicines and, therefore, established the 'qualification procedure' to give an advice and/or opinion on a biomarker or methodology and its acceptability for a specific use in pharmaceutical research and development [14]. To date, nine qualification opinions have been published by the EMA, enabling their use during clinical trials and drug development [14].

Challenges for the implementation of pharmacogenomics in drug development

Regulators are often confronted with challenges involved in translating data from pharmacogenomic studies into clinically relevant and meaningful product information, starting with the level of scientific evidence required to justify the inclusion of PG data in the product information.

The integration of genomic data in patient treatment requires evidence of consistency and size of measured

effects, medication compliance and phenoconversion [15]. A further regulatory challenge is the evaluation of the effect of ethnicity, especially in the context of global drug development and extrapolation of clinical trial genomic data from one population to another. A recent example provides the evaluation of carbamazepine-associated risk of skin reactions in association with the HLA-B*1502 allele in patients from some Asian populations and with the HLA-A*3101 allele in patients of European and Japanese descent [16].

Other critical issues for the further integration of pharmacogenomics into drug development, surveillance and clinical care include the feasibility of (genomic) testing in the clinical setting, e.g. test availability across the EU, its correct interpretation and the evaluation of the evidence of its clinical utility. Depending on where PG data are presented in the SmPC, PG testing could be required before treatment, with consequent liability implications for the healthcare professional [2]. This could have implications for patients' access to the appropriate therapy, e.g. in case the test is not available or there is neither competence nor enabling tools available to support the prescriber for the correct interpretation of the test. Finally, payers too need to be convinced that there is an added cost–benefit in the application of pharmacogenomic-guided treatment in clinical care (clinical usefulness) and, therefore, an appropriate health technology assessment (HTA) and reimbursement system needs to be in place.

With the inclusion of, for instance, pharmacogenomic testing in the form of companion diagnostics, regulatory, HTA and reimbursement decisions related to medicinal products become more complex. Particularly during times of economic constraints, the transparency and predictability of the regulatory system and of the elements key for the HTA evaluations are essential both for the sponsors and for the payers.

In support, the EMA has engaged in a pilot project of parallel scientific advice with HTA bodies [17] since 2010 that allows developers to receive simultaneous parallel feedback from both regulators and HTA bodies on their development plans for new medicines. The EMA, with the support of the European medicines regulatory network, has so far conducted 25 parallel scientific advice procedures with several HTA bodies taking part in this pilot project; a further six procedures are expected to start in 2014. In November 2013, the EMA held a workshop on parallel scientific advice with HTA bodies, collecting opportunities, challenges and concerns flagged from the stakeholders [18].

The advances in genomic science and technologies are also involved in transforming the paradigm of clinical development and clinical data gathering. Regulators and developers are confronted with the emergence of biomarker tests intended for precision medicine with existing drugs as well as adaptive trial designs [19] to provide the necessary evidence for the authorization of both drugs and diagnostics.

Potentially non-aligned life cycles of companion diagnostics and medicines add further complexity, and an adaptive reimbursement model needs to be established to guarantee the development of companion diagnostics for drugs already on the market [20]. The fact that these obstacles can be overcome has been demonstrated by the change of companion test for Herceptin from immunohistochemistry to fluorescence *in situ* hybridization [21].

In October 2012, the EMA hosted a workshop on 'Pharmacogenomics: From Science to Clinical Care', bringing all stakeholders together to discuss challenges, bottlenecks and benefits [22]. Discussion suggested that the quantity and quality of evidence for the integration of more pharmacogenomics in healthcare is improving [22], as is the awareness of pharmacogenomics and its acceptance as a potential tool to improve healthcare. The costs for genotyping are decreasing, and pharmacogenomic testing has become a valuable tool to reduce adverse drug reactions and improve the efficacy of certain selected drug treatments [23]. However, laboratories performing pharmacogenomic tests are still few in number, reflecting low clinical uptake. Declared reasons for the so-far rather limited clinical implementation of pharmacogenomic testing include lack of education and awareness [24], lack of prescriber-supportive tools, such as treatment algorithms including a genomics component, lack of proof of clinical usefulness and negative cost–effectiveness studies. Political challenges include the establishment of an adequate legal framework governing data protection [25], different bodies for central medicines regulation and device authorization, and heterogeneous healthcare systems across the EU.

Conclusion and outlook

With the recent drafting of two guidelines on pharmacogenomics during drug development and the postauthorization phase, respectively [3, 4], the EMA intends further to enable the potential of PG during drug development and surveillance and to gain insight into the associated scientific challenges and discuss potential solutions. The guidelines are expected to improve genomic data-informed drug development and clinical experience, thereby promoting understanding of interindividual drug response variations and, consequently, provide guidance towards more personalized treatments in the interest of the patient and public.

As novel '–omics' technologies such as next generation sequencing materialize and become more affordable, new scientific insight into DNA and RNA variants will emerge and will enable us to predict the influence of such

variations on drug response and interaction in a more precise way.

The role of epigenetics in addressing gaps between genomic traits and the response of the phenotype to the environment will gain importance and facilitate both the understanding of multifactorial diseases and the implementation of more personalized medicine to the benefit of patients and public health.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 ICH E15: definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories. Available at http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html (last accessed 7 December 2013).

2 European Commission guideline on summary of product characteristics (SmPC). Available at http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf (last accessed 7 December 2013).

3 EMA: guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500121954.pdf (last accessed 7 December 2013).

4 Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products, Draft. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/01/WC500160232.pdf (last accessed 14 March 2014).

5 Maliepaard M, Nofziger C, Papaluca M, Zineh I, Uyama Y, Prasad K, Grimstein C, Pacanowski M, Ehmann F, Dossena S, Paulmichl M. Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective. Nat Rev Drug Discov 2013; 12: 103–15. doi:10.1038/nrd3931.

6 European Medicines Agency (EMA). European public assessment reports. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 (last accessed 7 December 2013).

7 EMA product information: Xaluprine, mercaptopurine. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/002022/WC500124645.pdf (last accessed 7 December 2013).

8 EMA product information: clopidogrel Apotex, clopidogrel. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/001189/WC500029701.pdf (last accessed 7 December 2013).

9 EMA product information: Ziagen, abacavir. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/000252/WC500050343.pdf (last accessed 7 December 2013).

10 Innovation task force (ITF) at the European medicines agency (EMA). Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9 (last accessed 7 December 2013).

11 Emerging science at the EMA. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000339.jsp&mid=WC0b01ac05800baed8 (last accessed 7 December 2013).

12 Ehmann F, Papaluca Amati M, Salmonson T, Posch M, Vamvakas S, Hemmings R, Eichler HG, Schneider CK. Gatekeepers and enablers: how drug regulators Respond to a challenging and changing environment by moving toward a proactive attitude. Clin Pharmacol Ther 2013; 93: 425–32. doi:10.1038/clpt.2013.14.

13 EMA scientific advice procedure. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9 (last accessed 7 December 2013).

14 EMA qualification of novel methodologies for medicine development. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0 (last accessed 7 December 2013).

15 Shah RR, Shah DR. Personalized medicine: is it a pharmacogenetic mirage? Br J Clin Pharmacol 2012; 74: 698–721.

16 PhVWP monthly report on safety concerns, guidelines and general matters. July 2012 – Issue number: 1207. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/07/WC500130391.pdf (last accessed 7 December 2013).

17 Joint EMA scientific advice with HTA bodies. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000476.jsp&mid=WC0b01ac0580236a57 (last accessed 7 December 2013).

18 European Medicines Agency/health-technology-assessment-body workshop on parallel scientific advice in drug development. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/06/event_detail_000721.jsp&mid=WC0b01ac058004d5c3 (last accessed 7 December 2013).

19 Simon R, Roychowdhury S. Implementing personalized cancer genomics in clinical trials. Nat Rev Drug Discov 2013; 12: 358–69. doi:10.1038/nrd3979.

20 Fridlyand J, Simon RM, Walrath JC, Roach N, Buller R, Schenkein DP, Flaherty KT, Allen JD, Sigal EV, Scher HI. Considerations for the successful co-development of targeted cancer therapies and companion diagnostics. Nat Rev Drug Discov 2013; 12: 743–55. doi:10.1038/nrd4101.

21 European public assessment report (EPAR) for herceptin (trastuzumab). Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000278/human_med_000818.jsp&mid=WC0b01ac058001d124 (last accessed 7 December 2013).

22 Workshop on pharmacogenomics: from science to clinical care; Report of the workshop held on 8-9 October 2012 at the European Medicines Agency. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/11/WC500134968.pdf (last accessed 7 December 2013).

23 Patel JN, McLeod HL, Innocenti F. Implications of genome-wide association studies in cancer therapeutics. Br J Clin Pharmacol 2013; 76: 370–80.

24 Amstutz U, Carleton BC. Pharmacogenetic testing: time for clinical practice guidelines. Clin Pharmacol Ther 2011; 89: 924–7. doi:10.1038/clpt.2011.18.

25 European Commission DG Justice. European Commission justice data protection legislation. Available at http://ec.europa.eu/justice/data-protection/law/index_en.htm (last accessed 7 December 2013).